

# Comments on Weight of Evidence Evaluation

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Science and Strategies for Safe Environments



# No Consistent Evidence for Cancer

- Human data do not consistently show increased mortality from or incidence of cancer
- Effects in experimental animals are species-specific and not applicable to humans
- Mode-of-action data demonstrate effects in animals are not applicable to humans
- There is no concordance among human, experimental animal, and mode-of-action data

# Human Evidence

- No consistent associations between styrene exposure and mortality from or incidence of any cancer type, either within or among studies
- Lack of exposure-response relationships
- Concerns regarding co-exposures to known carcinogens and confounding
- A causal interpretation is not credible, and the standards of "limited" evidence are not met

# Animal Evidence

- Tumors observed in certain strains of only one species (mice) and at one tissue site (lung); mostly benign
- High background of this tumor; developed late in life in the presence of chronic cytotoxicity
- No tumor response in rats
- Animal evidence does not meet the standards of "sufficient" evidence

# Mechanistic Data

- Suggest a non-genotoxic mode of action for styrene that is based on local cytotoxicity and subsequent cell proliferation
- Highly species-specific
  - localized metabolism via cyp2f2 – a major pathway only in mouse lung
  - Human CYP2F1 not active toward styrene
- Not applicable to humans or other animals

# Weight-of-Evidence Analysis

- Human data don't meet "limited evidence"
  - No consistent responses among the human data of the kind that one would expect if there were true biological causation
- Animal data don't meet "sufficient evidence"
  - Only (some) mice, only inhalation
  - No generalizable response (even to rats)
- Mode of action in mice does not occur in rats; no indication it would occur in humans
- No common thread to link human, animal, and MOA data
- Styrene should be "Not Classifiable"